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## The Optimal Intensity of Vitamin K Antagonists in Patients With Mechanical Heart Valves: A Meta-analysis

I enjoyed the article by Vink et al. (1), which again revisits an old and most important clinical chestnut, but I have serious misgivings about their conclusions. Some years ago, we did a detailed and comprehensive analysis of 1,134 patients who had received St. Jude prosthetic valve(s) over a 13-year period (2). The follow up was 100% complete—4,936 patient years—and the study had a 60% post-mortem examination rate for early deaths.

The recommendation we made as the result of our analysis, namely that the INR should be kept between 2.5 and 3.0, is at complete variance with that of the authors. I believe that the problem arises from the fact that the target international normalized ratio (INR) range on which the authors focused may have no bearing whatsoever on the INR *at the actual time* of the anticoagulant-related complication. In contrast, we based our recommendations on the INR measured *at the actual time* of the anticoagulant-related complication, which we had in 88% and 58% of the major thromboembolic and hemorrhagic complications, respectively. Furthermore, in a more recent study (3), we found that at any given time 21.8% to 32.5% of patients were outside the target INR set for them; indeed, other authors have found an even greater number of patients (up to 52%) outside the target INR range (4).

It is essential therefore to base any recommendation regarding anticoagulation on an analysis of INR readings *at the actual time* of the anticoagulant-related complications rather than the target INR range, which is the ideal rather than the reality.

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## Anticoagulation Management of Patients With Prosthetic Valves

As authors of previous European guidelines on anticoagulation of patients after valve surgery and as members of a committee currently revising those guidelines, we are concerned to read the paper of Vink et al. (1) Their recommendation that all patients should be managed with an international normalized ratio (INR) of 3.0 to 4.5 reverses current trends to individualize antithrombotic management for each patient based on an assessment of their particular thromboembolic risk (2–4). Although having a “one size fits all” approach to anticoagulation management may have advantages for anticoagulation clinics, this approach will not benefit individual patients who may be exposed to the risks of unnecessarily high anticoagulation.

Their meta-analysis raises several concerns. First, meta-analysis is a technique for amalgamating data from randomized controlled trials (RCT) that have used the same methodology, not observational studies with different methodology. Second, reported thromboembolic rates are heavily influenced by definitions, data collection methods (prospective vs. retrospective), size and length of study, patient risk factors, concomitant surgery, and type of prosthesis (5,6). Other than the prosthetic type, these factors are not mentioned. Valve thrombosis rates are influenced by the number of patients who experienced anticoagulation interruption, to which most cases are related (7). Third, we question the use of target INRs rather than achieved INRs. Many events occur when the INR is outside the target range.

Fourth, retrospective conversion of prothrombin time ratios to INR has the potential to introduce huge errors. In American studies, it is highly unlikely that a single thromboplastin reagent would have been used for all patients in the study (8).

Finally, there is a lack of acknowledgment of the five published RCTs comparing different anticoagulation intensity (9–13). Although most of these RCTs have limited applicability because of their methodologies, all reached the conclusion that a higher intensity of anticoagulation did not reduce the incidence of thromboembolism. Four RCTs showed a higher incidence of bleeding with higher intensity anticoagulation. The only RCT not to show this effect used overlapping INR ranges and did not record events in the first three months (13).

Although Vink et al. (1) acknowledge that high-intensity anticoagulation results in a higher incidence of bleeding, they appear to minimize this danger. Use of a higher range of INR, 3.0 to 4.5, for all patients imposes an imperative for extremely tight INR control. High variability of INR, with >30% of INRs outside the range 2.0 to 4.0, is the strongest

predictor of reduced survival after valve replacement (14). Furthermore, thromboembolic and bleeding events are not equivalent in terms of mortality risk. The one-year survival after ischemic stroke is about 80%, whereas the one-year survival after intracerebral hemorrhage is only about 20% (15).

The paper of Vink et al. (1) reinforces the view of the Dutch Thrombosis Service since the mid-1980s that all mechanical valve patients should have an INR of 3.0 to 4.5, (16) However, it is scientifically unsound in its methodology, ignores evidence for a contrary view, including RCTs and current guidelines (2,4,17), and takes a big step backward from the modern practice that is based on individual risk stratification and risk-adjusted intensity of anticoagulation. We believe that their recommendations should not be followed.

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## REPLY

We appreciate the comments regarding our article (1). Dr. Takkenberg and colleagues have calculated mortality rates of the thromboembolic and bleeding complications and found no differences between high-intensity and low-intensity therapy with vitamin K antagonists. Unfortunately, only approximately 50% of the included studies reported on mortality rates. As a result, the mortality event rate is too low to draw any statistically confident conclusion. Therefore, it remains uncertain whether the results of this small number of studies would be representative for the total mortality rate of all studies analyzed in our meta-analysis.

Dr. O'Kane raised an important point about the target international normalized ratio (INR). We agree that it is more sound to evaluate the achieved INR rather than the target INR. However, as already mentioned in our article, most reports used for our analysis were based on an intention-to-treat INR range. Furthermore, Dr. O'Kane recommends an INR between 2.5 and 3.0 based on a single-center observational study, which unfortunately lacks information on the time spent in the target range and the achieved INR. In addition, a part of the study population in this study received dipyridole in combination with vitamin K antagonists, which increased the risk of bleeding complications (2).

Drs. Butchart and Gohlke-Bärwolf are confused when they state that meta-analyses can be performed only on randomized controlled trials. It should be clarified that meta-analysis is a statistical method defined as the quantitative analysis of two or more independent studies to integrate the findings. Studies used for meta-analysis can vary from randomized trials, non-randomized trials, or observational studies, and even from more than one of these types of studies (3).

Furthermore, they postulate that the reported thromboembolic rates are influenced by definitions, data collection methods, and patient characteristics. In our study, all events were analyzed according to the guidelines for reporting morbidity and mortality after cardiac valvular operations of Edmunds et al. (4), which minimize the potential for bias. Mean age at valve implantation and gender did not differ between the groups. Other characteristics were not specified